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PRINCIPAL INVESTIGATOR: Yoshio Nakamura, Ph.D.

CONTRACTING ORGANIZATION: University of Utah
Salt Lake City, UT 84112

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Yoshio Nakamura, Ph.D.

E-Mail: yoshi.nakamura@utah.edu

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14. ABSTRACT
Mind-body Bridging (MBB) has been shown to be an effective mind-body intervention for improving health outcomes in the management of disturbed sleep. In this prospective RCT, we evaluated the efficacy of sleep-focused mind-body bridging (MBB) compared with a sleep hygiene education control (SED) for improving sleep in Gulf War (GW) Veterans suffering from disturbed sleep and other co-existing symptoms. MBB (n=33) and SED (n=27) each comprised three weekly sessions. The primary outcome measure, Medical Outcomes Study-Sleep Scale (MOS-SS) was completed at baseline (pre-intervention), weekly during treatment, post-intervention and 3-month follow-up, while secondary measures for PTSD, depression, fatigue, quality of life, symptom severity, and mindfulness were completed at Baseline, Post-intervention and 3-month Follow-up. Clinician-administered assessments for sleep and co-occurring physical and psychological health status were conducted at baseline and post-intervention. Results demonstrated that MBB was significantly more efficacious than SED in reducing sleep problems at Follow-up. Additionally, self-reported PTSD, depression and fatigue symptoms significantly improved in MBB compared with those in SED, mostly at follow-up. Consistently higher percentages of GW Veterans in MBB experienced improved symptoms at the clinical evaluation in comparison with those Veterans in SED. These findings provide encouraging evidence that sleep-focused MBB is an efficacious intervention program that can improve both sleep and co-occurring symptoms in GW Veterans.

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1. **Front Cover**
2. **Standard Form (SF 298)**
3. **Table of Contents**

Table of Contents

Investigating clinical benefits of a novel sleep-focused mind-body program on Gulf War Illness (GWI) symptoms: An exploratory randomized controlled trial

Principal Investigator:	Yoshio Nakamura, PhD
Investigators and Research Study Staffers:	Gary Donaldson, PhD Yuri Kida, MSW David Lipschitz, PhD Samuel Williams, BA Richard Landward, MSW Don Glover, PhD, MSW Ashok Tuteja, MD Gavin West, MD

Corresponding Author:
Yoshio Nakamura, Ph.D.
Utah Center for Exploring Mind-Body Interactions
Pain Research Center, Department of Anesthesiology
University of Utah School of Medicine
615 Arapeen Drive, Suite 200
Salt Lake City, UT 84108
Email: yoshi.nakamura@utah.edu

ABSTRACT

Mind-Body Bridging previously has been shown to be an effective mind-body intervention program for improving health outcomes in the management of disturbed sleep. In this prospective, randomized-controlled trial, we evaluated the efficacy of sleep-focused Mind-Body Bridging (MBB) compared with a sleep hygiene education control (SED) for improving sleep in Gulf War Veterans suffering from disturbed sleep and other co-existing symptoms. MBB (n=33) and SED (n=27) treatment each comprised three weekly sessions. The primary outcome measure, Medical Outcomes Study-Sleep Scale (MOS-SS) was completed at baseline (pre-intervention), weekly during treatment, post-intervention and 3-month follow-up, while secondary outcome measures for PTSD, depression, fatigue, quality of life, symptom severity, and mindfulness were completed at Baseline, Post-intervention and 3-month follow-up. Clinician-administered assessments for sleep and co-occurring physical and psychological health status were conducted at baseline and post-intervention. Results demonstrated that MBB was significantly more efficacious than SED in reducing sleep problems at follow-up. Additionally, self-reported PTSD, depression and fatigue symptoms significantly improved in MBB compared with those in SED, mostly at follow-up. Consistently higher percentages of GW Veterans in MBB experienced improved symptoms at the clinical evaluation, as compared to Veterans in SED. These findings provide encouraging evidence that sleep-focused MBB is an efficacious intervention program that can improve both sleep and co-occurring symptoms in GW Veterans.

Key words: Gulf War Veterans; sleep disturbance; mind-body intervention; Mind-Body bridging; mindfulness; awareness training; sleep education

INTRODUCTION

Approximately 700,000 United States military service members were deployed in the first Persian Gulf War (GW). Many of these GW Veterans continue to experience a complex of troubling chronic symptoms, at a significantly higher rate than that associated with non-Veterans or non-deployed Veterans. This symptom complex, known as Gulf War Illness (GWI), includes chronic headache, cognitive difficulties, widespread pain, unexplained fatigue, sleep disturbance, memory and concentration problems, respiratory disorders, and gastrointestinal symptoms. Sleep disturbance is one of the four frequent symptoms of Chronic Multisystem Illness along with chronic pain, cognitive dysfunction and fatigue. Currently, there is no proven effective complementary and alternative program for treating the co-morbid symptom pattern of sleep disturbance and GWI. Lack of sleep is known to lead to cognitive impairment and worsening of some typical GWI symptoms such as pain and fatigue. Restorative sleep is an integral part of healing that veterans need to activate in recovering from their illness and regaining increased quality of life. A pressing need exists to develop and refine a new interventional approach by which GW veterans can master behavioral and cognitive skills in regulating emotional and psychological dysregulated states that accompany GWI, including disturbed sleep.

CAM therapies such as mind-body interventions have been increasingly used to improve sleep, as well as general health and well-being. The last few decades have seen development of mind-body interventions that focus on the power of “mental training” in regulating mental and physical health conditions (Begley, 2007), including Mindfulness-Based Stress Reduction (MBSR; (Kabat-Zinn, 1991) and Mindfulness-Based Cognitive Therapy (MBCT; (Teasdale, et al., 2002; Teasdale, et al., 2000). Both MBSR and MBCT have emerged as effective treatment/management programs for medical conditions such as cancer (Matchim, Armer, & Stewart, 2011), mood disorders (Hollon & Ponniah, 2010), and disturbed sleep (Gross, et al., 2011; Winbush, Gross, & Kreitzer, 2007).

Another novel mind-body intervention showing promise as a treatment for sleep disturbance is Mind-Body Bridging (MBB; Block & Block, 2005, 2007). MBB is an awareness training program that comprises experiential exercises to help individuals be more aware of their senses in order to calm their minds and relax their bodies. While a more comprehensive explanation of MBB can be found in Nakamura et. al. (2015), briefly, MBB utilizes awareness practices that can help individuals transform disharmonious mind-body states into more adaptive ones. MBB helps individuals reduce self-centeredness, through “bridging” activities, which are experiential exercises used to direct attention towards the senses (tune into the senses), and “mind-body mapping” techniques, which are written exercises in which free-association thoughts can reveal specific thought patterns termed “Requirements.” Requirements are described as expectations an individual has about how she or he and the world “should be” at a particular moment. Requirements that are excessively self-centered and not fulfilled can lead to a dysfunctional mind-body state, with negative health

consequences. Defusing Requirements through mind-body mapping provides an opportunity for individuals to develop more balanced, less volatile mental states. MBB addresses the underlying cause of resistances to clarity as mental perturbations stemming from an individual's fixed idea of who they are, described as the "Identity System" (IS) in MBB teaching terminology. Learning to "rest the IS" helps individuals attain less reactive states associated with thoughts, feelings and emotions, and events that occur in their lives. MBB is easy to learn and implement, and benefits can accrue rapidly. Thus, MBB might become a viable clinical intervention for the treatment of those health conditions that are especially prone to mental agitations, including sleep disturbance, depression, and anxiety, and PTSD, many of which are present in Veterans with GWI.

The major aim of the proposed exploratory study was to investigate therapeutic benefits of a brief sleep-focused mind-body program on 1) reducing sleep disturbance and 2) attenuating other GWI symptoms. The sleep-focused program, based on Mind-Body Bridging (MBB), previously has proven effective in reducing sleep problems and improving co-occurring symptoms (such as self-reported PTSD and depression symptoms) in two pilot randomized controlled studies of non-GW Veterans with sleep disturbance (Nakamura et al. 2011) and cancer survivors with sleep disturbance (Nakamura et al. 2013). This suggests that sleep-focused MBB might significantly improve care of veterans with GWI. Building on findings from our previous pilot study of MBB with Veterans (Nakamura et al 2011), we conducted this prospective randomized exploratory clinical trial to evaluate the efficacy of sleep-focused MBB as compared with sleep education (SED) in GW Veterans with sleep disturbance and unrelieved GWI symptoms.

METHODS

Study Participants

The study population comprised Gulf War Veterans who were 18 years or older in the combat theater during the Persian Gulf War, from August 1990 through January 1991. Prospective participants for the exploratory study consisted of Gulf War Veterans who presented to primary care at the VA Salt Lake City Health Care System (VASLCHCS) with a) self-reported sleep disturbance and b) at least one or more unrelieved symptoms typical of GWI including: unexplained fatigue, chronic headaches, joint or muscle pain, cognitive difficulties, memory and concentration problems, shortness of breath, and chronic gastrointestinal (GI) symptoms that are typical of Irritable Bowel Syndrome (these GI symptoms included chronic diarrhea, excessive gas, and abdominal pain).

The inclusion criteria used here were consistent with our case definition of Gulf War Illness used in the current study - the case definition of GW illness was operationalized as follows: Gulf War (GW) veterans who present with self-reported sleep disturbance and at least one or more of unrelieved symptoms that are typical of GWI.

Patients were excluded from the study if they had delayed sleep phase syndrome, advanced sleep phase syndrome, or narcolepsy, were terminally ill, had active suicidal ideation, had a highly unstable medical or psychiatric condition (any condition requiring hospitalization imminently or within 3 months prior to study), Parkinson's Disease, dementia of any cause, frequent nocturia, or severe cognitive difficulties. A clinical evaluation conducted by a physician's assistant at pre-assessment ensured that exclusionary sleep disorder conditions and other symptoms included above were not identified in GW Veterans who wished to participate in the study. Participants could be on any sleep medications that had been previously prescribed.

Participants were not excluded from participating in the study if they presented with central or obstructive sleep apnea, periodic limb movement disorder, or sleep-disordered breathing with any restrictive or obstructive pulmonary disease, but these illnesses were used as part of a stratified randomization procedure (see Study Design), to ensure that the distribution of GW Veterans with any of these conditions was not skewed across the two groups.

The Institutional Review Boards at the University of Utah and the Salt Lake City Veterans Administration facility approved all aspects of the study. ClinicalTrials.gov Identifier for the study is NCT01543997

Study Design

This study was a prospective, randomized study in which 60 participants were assigned to one of two parallel arms: a) Mind-Body Bridging (MBB; experimental condition; n = 33) or b) Sleep hygiene education (control condition; n = 27). Participants were computer-randomized in blocks of 4 to one of the interventions, stratified by central or obstructive sleep apnea, periodic limb movement disorder, and/or sleep-disordered breathing with any restrictive or obstructive pulmonary disease. They only found out their treatment assignment when they arrived to attend their first MBB or SED session. The study was conducted between May 2012 and April 2015.

Interventions

Participants were randomized to either MBB or Sleep Hygiene Education (SED), comprising three weekly sessions, conducted once per week for 3 consecutive weeks. All treatment sessions were in a group format and conducted at VA Salt Lake City Health Care System.

Sleep Hygeine Education (SED): The SED intervention provided standard educational lectures and group discussion on sleep hygiene, focusing on helpful tips to deal with difficulties related to sleep. The program did not teach any specific skills to deal with their arousal, mood, or sleep. The SED program served as an active control group designed to control for non-specific factors associated with being in a supportive group and interactions with a therapist. The intervention was provided by a VA physician assistant.

Mind-Body Bridging (MBB): MBB and specifically the sleep-focused MBB program have been described previously (Nakamura, Lipschitz, Kuhn, Kinney, & Donaldson, 2013; Nakamura, Lipschitz, Landward, Kuhn, & West, 2011). Briefly, participants were taught MBB concepts and how these could assist them in dealing with persistent sleep problems. The MBB tools included bridging exercises, identifying what expectations they had of the world (Requirements), and recognizing an active Identity System, to help their sleep improve. MBB was taught by licensed clinical social workers who had received certification training in MBB and used MBB in clinical care for their clients.

MBB is focused on teaching experiential skills that participants can use in regulating awareness and reactions to cognition and emotions that arise in response to external and/or internal triggers. During Session 1, participants were taught MBB concepts, and learned how to use MBB tools to help them fall asleep more quickly and sleep more soundly. These tools included specific “bridging” techniques to use when trying to fall asleep, such as paying attention to sounds or feeling sensations of the bed sheets, etc. In Session 2, participants learned how to reduce daytime stress and how to free themselves from intrusive thoughts, feelings and emotions. In Session 3, participants learned how to understand and identify Requirements. For maximal effectiveness, MBB participants were encouraged to understand these principles and practice MBB techniques at any time throughout the day and right up to the time when they went to bed, as well as after waking up and while trying to get back to sleep.

Participants who missed two of the three sessions were considered as not completing the treatment program. However, they were invited back to both post and follow-up assessments and evaluations.

Study Procedures

Screening of participants was conducted at VASLCHCS clinics or over the phone. Prospective study participants completed a brief screening health history questionnaire, as well as the MOS sleep scale sleep problems index II (SPI-II). To be eligible, they needed to score 35 or higher on the SPI-II. After they were determined to be provisionally eligible, they underwent informed consent and were scheduled for a comprehensive physical evaluation. During the evaluation, a physician assistant (PA) went through their medical history and performed physical examinations to ensure that the participant met study eligibility.

Participants completed self-report questionnaires for sleep and other outcome measures, including depression, PTSD, quality of life (QOL), fatigue, cognitive functioning, gastrointestinal problems, general symptom severity, and mindfulness. For sleep, measures were collected at baseline (Pre), weekly during treatment (Week 2, 3), post-intervention (Post), and at the 3-month follow-up (referred to as “Foll-up” on some tables below). For the remaining measures, data were collected at Pre, Post and Follow-up. In addition, saliva samples were collected to assess cortisol and alpha-amylase, as indicators of Hypothalamic-Pituitary-Adrenal axis functioning and

sympathetic drive, respectively. Saliva samples were collected from subjects at Pre, Post and Follow-up, but data are still being processed and analyzed. Prior to the first session, but after participants found out to which group they had been assigned, they answered a question asking about their expectations of treatment benefit.

During Post assessment, the participants were re-evaluated by a PA via a second physical evaluation, the same as that administered before beginning the study to assess sleep and co-occurring symptoms. The assessment also determined if the participant's condition had improved, worsened or remained the same as that reported during the baseline assessment.

For those participants who dropped out before completing treatment, the study team attempted to contact them to collect self-report data from them at the post and 3-month follow-up assessments.

Outcome Measures

Participants in both MBB and SED groups completed all the self-report outcome measures, as described below.

Expectation for treatment benefit
Before and after participants learned to which group they had been randomized (but just before attending their first group session), they were asked to what extent they thought the treatment they would receive would help improve their sleep problems and other symptoms. They recorded their responses on an 11-point Likert-like scale in which 0 reflected that it was not at all likely, and 10 reflected that it was highly likely to improve their symptoms.

Primary Outcome Measure

Medical Outcomes Study - Sleep Scale (MOS-SS)
The MOS-SS is a validated 12-item brief questionnaire, which assesses sleep difficulties (Hays, Martin, Sesti, & Spritzer, 2005), and has been employed in previous sleep studies examining MBB (Nakamura, et. al., 2013; Nakamura, et. al., 2011). The present study utilized the Sleep Problems Index II (SPI-II) subscale, a composite score comprising MOS-SS subscales, sleep disturbance, sleep adequacy, and daytime somnolence. In the present study, Cronbach's alpha coefficient for SPI-II was .67.

Secondary Outcome Measures

Medical Outcomes Study Short Form-36 (MOS SF-36)
Quality of Life (QOL was measured by Medical Outcomes Study Short Form-36 (MOS SF-36). We were interested in determining MBB's relative efficacy using a standard measure of Quality of Life (QOL), such as the SF-36, to assess functional status. SF-36 is a self-report inventory that measures a person's perception of his/her overall health

status in the past 4 weeks, as it relates to 8 health domains. An adapted form, SF-36V, for Veterans (now termed VR-36) consists of the same eight sections as the MOS SF-36, including physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health perceptions (GH), energy/vitality (V), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH). The psychometrics of the SF-36 has been extensively studied with strong results. The reliability of the eight scales and two summary measures has been estimated using both internal consistency and test-retest methods. With rare exceptions, published reliability statistics have exceeded the minimum standard of 0.70 recommended for measures used in group comparisons in more than 25 studies (Tsai, Bayliss, & Ware, 1997). In the present study, Cronbach's alpha coefficient for SF-36V Total Score was .95.

PTSD Check List – Military (PCL-M)

Post-Traumatic Stress Disorder symptoms were assessed via the PTSD Check List – Military (PCL-M), a 17-item self-report measure that was constructed to be used with male and female Veterans to assess military-related PTSD. For each item, respondents rate how much they were "bothered by that problem in the past month." The PCL-M is very brief, requiring less than 10 minutes, and reliability evidence is very good. Items are based on DSM-IV criteria and are rated on a 5-point Likert-type scale. PCL-M asks questions about "stressful (military) experience." (Weathers, Litz, & Herman, 1993) The PTSD checklist has been shown to have internal consistency and to correlate well with other measures of PTSD. (Blanchard, Jones-Alexander, Buckley, & Forneris, 1996; Cook, Elhai, & Arean, 2005) In the present study, Cronbach's alpha coefficient for PCL-M Total Score was .92.

Center of Epidemiological Study-Depression Scale (CES-D)

Depression was measured by the real-time assessment method as noted above and two self-report inventories: Center of Epidemiological Study-Depression Scale (CES-D)(Radloff, 1977) and the Mental Health scale of the Short Form Health Survey (SF-36) (Ware & Sherbourne, 1992) (see above for the psychometric information). The CES-D is a 20-item self-report inventory to assess depressive symptomatology. Respondents are asked to indicate how frequently they experienced each symptom in the past week, ranging from 0 (less than one day) to 3 (5 to 7 days). The total possible score ranges from 0 to 60, reflecting both the number of symptoms and the frequency of their occurrence. The internal consistency of the CES-D has been reported to be from .84 to .90 (Radloff, 1977). In the present study, Cronbach's alpha coefficient for CES-D Total Score was .62.

Multidimensional Fatigue Inventory (MFI)

The Multidimensional Fatigue Inventory (MFI) is a 20-item self-report instrument designed to measure key aspects of fatigue. It covers the following dimensions: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity. This instrument has been tested for its psychometric properties in various patient and general populations. The instrument has been found to have good internal consistency, with an average Cronbach's alpha coefficient around 0.84, which also was observed in the present study.

Cognitive Failures Questionnaire (CFQ)

The Cognitive Failures Questionnaire (CFQ) was used to measure participants' self-reported frequency of subjective cognitive failures in daily life. As a self-report questionnaire, the CFQ originally was devised to measure perception, memory, and motor lapses in daily life. (Broadbent, Cooper, FitzGerald, & Parkes, 1982) CFQ scores have been found to correlate with some psychiatric symptoms associated with stress; hence, high scores on the CFQ are considered by some to be an indicator of increased vulnerability to stress. Individuals scoring high on the CFQ report higher levels of anxiety and depression, both cross-sectionally (Merckelbach, Muris, Nijman, & deJong, 1996) and longitudinally (Power, 1988). This effect may be particularly evident in combination with exposure to stressful environments, suggesting that individuals scoring high on the CFQ are less successful at developing active coping strategies in dealing with stress. The lack of active coping strategies may be explained on the basis of a less effective management of attentional capacity, possibly putting individuals at risk of developing depressive symptoms. In the present study, Cronbach's alpha coefficient for CFQ Total score was .92.

Brief Symptom Inventory (BSI-18)

Psychological symptoms were assessed using the Brief Symptom Inventory (BSI-18), a short form of Symptom Check List-90 (SCL-90-R).(Derogatis, 1993) The BSI-18 is validated and has 18 items (six each on somatization, depression, and anxiety dimensions). The global severity index summarizes the respondent's overall level of distress. Each item response is scored 0-4. The psychological symptoms and composite scores from BSI-18 test correlate highly (i.e., >0.90) with SCL-90-R. In the present study, Cronbach's alpha coefficient for BSI-18 Total Score was .88.

Five-Facet Mindfulness Questionnaire (FFMQ)

The FFMQ was developed from an analysis of five recently developed mindfulness questionnaires and contains five clear, interpretable facets of mindfulness. (Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006) Since MBB is based on awareness practices, it is highly informative to determine the degree to which mindfulness is cultivated by MBB for sleep management. In the present study, Cronbach's alpha coefficient for FFMQ Total Score was .91.

Clinical Evaluation by Physician Assistant

Before (Pre) and following completion (Post) of the interventions, participants were evaluated by a Physician Assistant to ascertain whether they experienced changes in the status of various symptoms that they have been suffering from.

Statistical Analyses

For the primary outcome measure of sleep, we conducted a mixed effects model analysis of covariance (ANCOVA), in which pre-randomized time points Pre and Week 1 served as the covariates. Treatment and Period were categorical factors. We conducted analyses on both the raw scores and transformed z scores to evaluate if the

data were normally distributed. If there was no differences in results of the ANCOVAs, only the raw score results were reported.

Initially, we determined the covariance structure for each outcome measure, and used the covariance structure that generated the best Bayesian Information Criterion (BIC; a smaller number is better) in the Treatment by Period factorial. The full factorial model, comprised the fixed variables, Treatment (MBB, SED), Period (Week 2, Week 3, Pre, Post and Follow-up), and Treatment by Period interaction (significant at $p < 0.05$). To gain insight into the magnitudes of treatment effects at each time point and within each group, we examined customized contrasts within and between the two treatments at Post and Follow-up, adjusted for (Pre) baseline and Week 1 (collected before the intervention phase of the study had begun). ANCOVAs are conducted in clinical trials to ensure that intervention groups are adjusted for baseline differences, to allow for robustness in comparisons between treatments at post-randomization. Mixed effects analyses include all observations of each dependent variable, providing an "intent-to-treat" approach for missing data. In this way, no observations are discarded and no data are imputed. Under the model's assumptions, the algorithm chooses parameter estimates generating the highest probability for all the data observed. The maximum-likelihood effect estimates are fully correct even if there is systematic unequal dropout conditional on baseline observations (Donaldson & Moinpour, 2005; Little & Rubin, 2002).

For all secondary outcome measures, an identical ANCOVA statistical analysis was conducted, but with only a single covariate (baseline); the post-randomization time points were Post and 3-month follow-up.

Clinical assessment: To evaluate mean differences in clinician-assessed symptoms between the two groups, we calculated mean proportions of participants exhibiting improvement, worsening or no change in each symptom at Post.

RESULTS

Participant Attendance

A total of 1,898 Veterans were contacted either by letter, telephone, or a VASLCHSC clinician (nurse, LPN) and asked if they are a First Gulf War Veteran, if they have any sleep problems, and if they would like to participate in a GW sleep study. Figure 1 provides an indication of the number of individuals who were screened (n=160) for the study, and how many were enrolled and were present at Post and Follow-up, for each intervention. Of the initial 60 participants, who were randomized to one of the two interventions investigated in the study (SED n=27; MBB, n=33), 57 participants completed the intervention, indicated by their attending at least two sessions (SED, n= 26, 96.3%; MBB, n= 31, 93.9%). A total of 55 completed Post assessment (SED, n=26, 93.9%; MBB, n= 29, 87.9%), and 49 completed Follow-up assessment (SED, n= 25, 92.6%; MBB, n= 24, 72.7%) self-report assessments.

Demographics and baseline characteristics

Table 1 shows demographics and baseline measures of the two groups of participants before randomization. Ages ranged from 39 to 69 (overall mean age=50.7, SD=7.3). Participants were predominantly white (88.0%) and male (89.9%). African Americans comprised 7.0% (n = 4) and Hispanics 8.6% (n = 5) of the sample. Baseline characteristics were generally balanced between the two groups.

Primary Outcome Measure

Sleep - MOS-SS Sleep Problems Index II (SPI-II):

As depicted in Figure 2, reductions in SPI-II occurred during treatment (Week 2, Week 3) and post-treatment (Post, Follow-up) in both interventions, as compared with baseline (baseline covariate, 63.41, as indicated by the horizontal line in the figure). There were similar reductions in SPI-II in both groups during the treatment period; however, at Follow-up, the MBB group showed greater improvements in sleep than did the SED group.

The ANCOVA revealed that adjusted mean SPI-II scores were no different for the Treatment effect ($F(1, 57.07) = 1.03$, p=.32). However, customized contrasts for comparisons between the two interventions were different at Follow-up ($F(1, 180.54) = 4.04$, p=.046), in which MBB sleep problems declined to a greater extent than did those for SED. Within group analyses indicated that both interventions reduced sleep problems at Post and Follow-up, with adjusted mean SPI-II score improvements for SED of 14.69 ($t(169.30) = 5.30$, p<.001) at Post and 12.63 ($t(172.70) = 4.48$, p<.001) at Follow-up, and adjusted mean SPI-II score improvements for MBB of 16.88 ($t(176.80) = 6.49$, p<.001) at Post and 20.70 ($t(188.73) = 7.29$, p<.001) at Follow-up, as compared with the baseline covariate score of 63.41.

Table 2 presents SPI-II unadjusted raw means and 95% Confidence Intervals (CIs) for the two treatment groups at Pre, Week 2, Week 3, Post and Follow-up (referred to on table as Foll-up). An effect size estimate for the difference between the two interventions at Post was .38, and Follow-up was .70 (see first section of Table 2). These analyses indicate that both interventions showed significant reductions in sleep problems at Post and Follow-up time points, but there were significant improvements in MBB compared with that of SED, especially at Follow-up.

Table 2 also provides unadjusted means and 95% CIs for the other MOS-SS subscales at the same time points to that of SPI-II. In these subscales, the ANCOVAs revealed no significant Treatment effect. However, as was identified for SPI-II, for within intervention analyses, other MOS-SS subscales indicated significant improvements at post-intervention (comprising Post and Follow-up) compared with baseline, including, Sleep Problems Index I (SED: change score = 14.08 (t(94.30) = 6.03, p<.001; MBB: change score = 18.85 (t(108.20) = 8.31, p<.001), Sleep Disturbance (SED: change score = 16.52 (t(111.36) = 5.97, p<.001; MBB: change score =23.71 (t(132.30) = 8.85, p<.001), Somnolence (SED: change score = 16.09 (t(91.23) = 6.87, p<.001; MBB: change score = 16.60 (t(108.38) = 7.46, p<.001), Shortness of Breath (SED: change score = 14.83

(t(77.83) = 4.16, p<.001; MBB: change score = 15.32 (t(89.72) = 4.58, p<.001), Sleep Adequacy (SED: change score = 3.70 (t(83.43) = 1.11, p<.27); MBB: change score = 10.41 (t(96.88) = 3.31, p=.001) and Snoring (SED: change score = 10.29 (t(84.11) = 2.64, p=.01; MBB: change score = 5.42 (t(95.88) = 1.4, p<.17)).

Secondary Outcome Measures

PTSD symptoms – PCL-M: Figure 3a shows adjusted mean PCL-M total scores, indicating the effects of SED and MBB on PTSD at Post and Follow-up. Adjusted mean PCL-M scores in MBB decreased at both time points compared with the baseline covariate (indicated by the dashed horizontal line in the figure), to a greater extent than those in SED.

Based on the ANCOVA, Treatment (*F*(1, 56.42) = 4.50, *p*=.038,) was significant, reflecting that MBB was more effective than SED in decreasing PCL-M scores. Treatment x Period interaction (*F*(1, 54.43 = .031, *p*= .86) was not significant. Customized contrasts for comparisons between the two interventions were not different at either Post or Follow-up. Additionally, at both Post and Follow-up, adjusted mean total score improvements of 3.30 (*t*(99.00) = 2.24, p=.03) and 5.45 (*t*(101.13) = 3.45, *p*=.001), respectively from the baseline covariate value (49.34), were noted for MBB. Although not significant, adjusted mean total score improvements of .55 (*t*(97.88) = .36, p=.72) at Post and 2.08 (*t*(98.62) = 1.34, *p*=.19) at Follow-up, from the baseline covariate value (49.34), were noted for SED.

An effect size estimate for the difference between the two interventions at Post was .07, and Follow-up was .19 (see first section of Table 3). Table 3 shows unadjusted PCL-M means and 95% CIs for the two treatment groups at Pre, Post and Follow-up. Overall, the findings indicate that MBB reduced self-reported PTSD symptoms more significantly than SED. This indicates that sleep-focused MBB may be efficacious for decreasing self-reported PTSD symptoms in GW Veterans.

Depression - CES-D: Figure 3b shows adjusted mean CES-D total scores, indicating the effects of SED and MBB on depression at Post and Follow-up. Mean CES-D scores in the MBB group decreased at Follow-up compared with the baseline covariate (indicated by the dashed horizontal line in the figure), to a greater extent than those scores in SED.

Based on the ANCOVA, both Treatment (*F*(1, 47.85) = 1.91, *p*=.17) and Treatment x Period interaction (*F*(1, 44.20) = 3.21, *p*=.08) were not significant. However, customized contrasts for comparisons between the interventions were different at Follow-up (*F*(1, 93.70) = 4.44, p=.038), in which CES-D mean score in MBB was lower than that in SED. Within the MBB group at Follow-up, an adjusted mean CES-D total score improvement of 2.94 (*t*(96.14) = 2.35, *p*<.02) from the baseline covariate value of 26.13, was noted, while an adjusted mean CES-D total score improvement of .81 (*t*(91.15) = .64, *p*<.52) for SED was not significant.

An effect size estimate for the difference between the two interventions at Post was .08, and Follow-up was .71, reflecting that MBB showed greater improvement than SED at Follow-up (see second section of Table 3). Table 3 shows unadjusted CES-D means and 95% CIs for the two treatment groups at Pre, Post and Follow-up. Overall, the results indicate that sleep-focused MBB reduced self-reported depression symptoms in these GW Veterans more significantly than SED, especially at Follow-up.

Fatigue – Mental Fatigue Subscale of MFI:

Figure 2d shows adjusted mean mental fatigue scores for each intervention at Post and Follow-up, indicating the effects of SED and MBB on mental fatigue. Mean mental fatigue scores were lower than the baseline covariate (indicated by the horizontal line in the figure) at Post in SED, and at both Post and Follow-up in MBB.

Based on the ANCOVA, Treatment ($F(1, 49.47) = 1.50$, $p=.23$) was not significant, while Treatment x Period interaction ($F(1, 44.37 = 4.89$, $p= .03$) was significant. Customized contrasts for comparisons between the two interventions were different at Follow-up ($F(1, 68.58) = 3.90$, p=.05), in which the mean mental fatigue score for MBB was lower than that for SED. Additionally, for the SED group, adjusted mean mental fatigue score improvement from the baseline covariate value (17.74) at Post was 1.46 ($t(63.22) = 2.51$, p=.02) and at Follow-up was .36 ($t(65.12) = .61$, p=.54). For the MBB group, it was 1.66 ($t(64.81) = 3.00$, $p=.004$) and 1.99 ($t(72.09) = 3.44$, $p=.001$), at Post and Follow-up respectively, from the baseline covariate value (17.74). An effect size estimate for the difference between the two interventions was .18 at Post, and was .47 at Follow-up, reflecting that MBB showed greater improvement in mental fatigue than SED at Follow-up (see Table 3). Table 3 shows unadjusted MFI mental fatigue subscale means and 95% CIs for the two treatment groups at Pre, Post and Follow-up. Overall, the results indicate that MBB reduced self-reported mental fatigue symptoms more significantly than did SED, specifically at Follow-up.

Other Secondary Outcome Measures

Table 3 displays unadjusted means and 95% CIs for other secondary outcome measures and subscales. As shown in the Table, there were no significant treatment effects based on the ANCOVAs for the Quality of Life measures on the SF-36V (Total Score and Pain subscale scores are listed separately), Brief Symptom Inventory (psychological symptoms), Multi-dimensional Fatigue Inventory (General Fatigue subscale is listed as well as overall inventory score), Cognitive Failure (CFQ) Total Score, or the FFMQ Total Score (mindfulness).

However, in some of these outcome measures, there was a significant reduction in symptoms at post-intervention (comprising Post and Follow-up). For SED, the reduction was in the CFQ (change score = 8.11, ($t(35.71) = 3.14$, p=.003). For MBB, there were reductions in the CFQ (change score = 5.47, ($t(39.19) = 2.49$, p=.02), in the MFI General Fatigue (change score = 1.43, ($t(50.10) = 2.74$, p=.009), and in the FFMQ (change score = 5.67, ($t(56.85) = 2.17$, p=.03).

Physical and Psychological Evaluations

The results of the clinician-administered sleep assessment are presented in Table 4. These descriptive data depict the extent to which symptoms worsened, remained the same, or had improved at Post compared to baseline, for those participants who completed the Post clinical evaluation. These results indicate that a larger percentage of GW veterans in the MBB group showed improvement in a number of physical and psychological symptoms, in comparison with those in the SED group.

CONCLUSIONS

The present RCT study was conducted to comprehensively explore potential benefits of a novel mind-body intervention program, Mind-Body Bridging, designed to improve sleep for Gulf War Veterans suffering from disturbed sleep and co-existing symptoms typical of Gulf War Illness.

First, sleep-focused MBB was efficacious in reducing disturbed sleep in comparison with the control, especially at Follow-up. Furthermore, sleep-focused MBB also was efficacious in decreasing self-reported outcomes of PTSD, depression, and mental fatigue. The sleep-focused MBB program offered in this study consisted of just three weekly sessions, so it is very encouraging to see that participating GW Veterans could use the MBB skills they learned to improve their sleep as well as other GWI-associated symptoms. Some further improvements were observed at Follow-up, indicating that potential benefits from sleep-focused MBB could last for at least three months.

These findings provide strong evidence that sleep-focused MBB may be able to serve as a front-loaded intervention program for helping GW Veterans manage the complex web of GWI symptoms, helping them along the path of recovery. MBB is relatively easy to teach and learn quickly, so it may be more cost-effective than other mind-body interventions. A larger RCT study would be required to more firmly establish the evidence base for MBB, with the goal of contributing to improved clinical care for GW Veterans.

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Figure 1. Study Flow

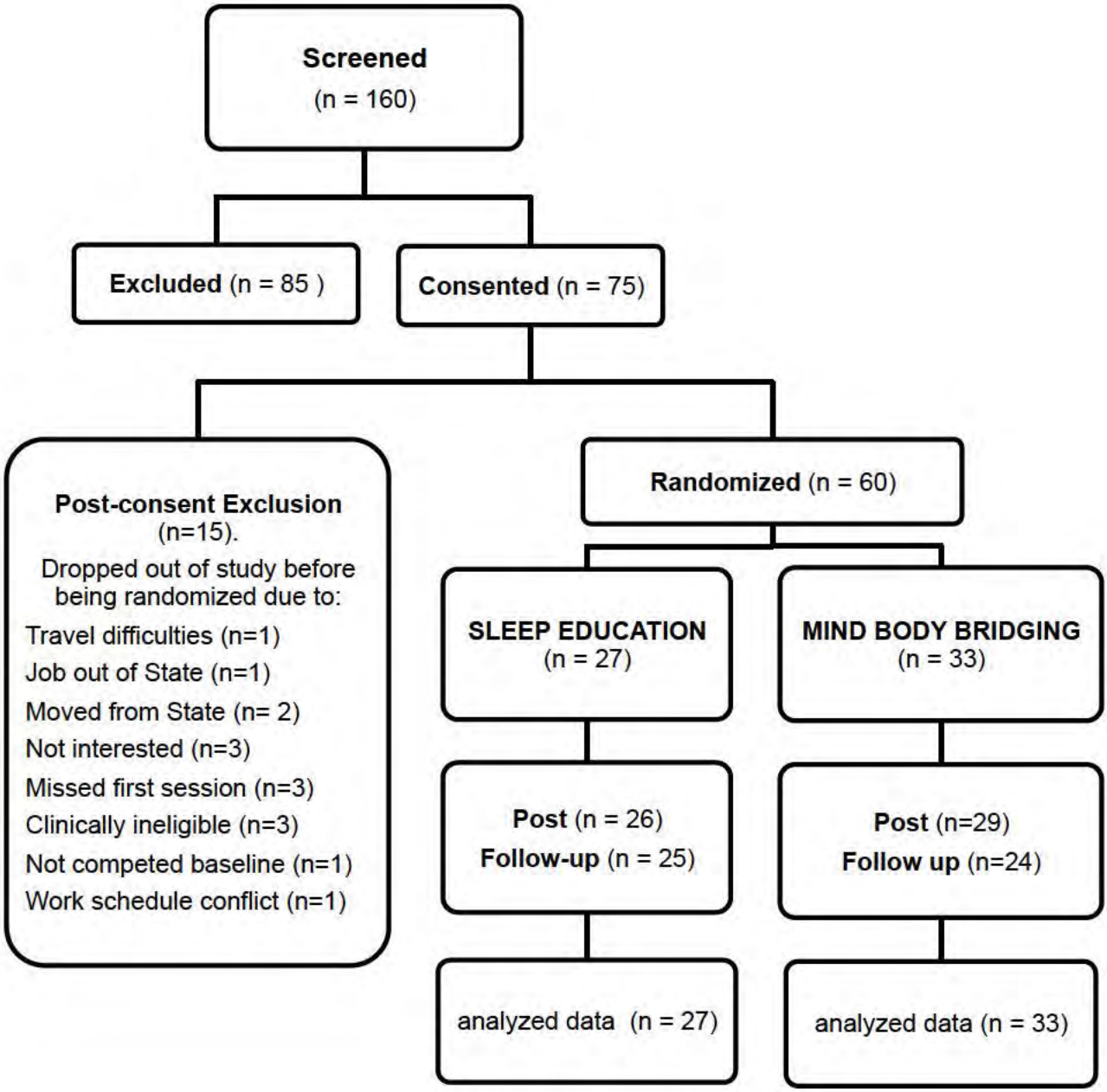

Figure 2

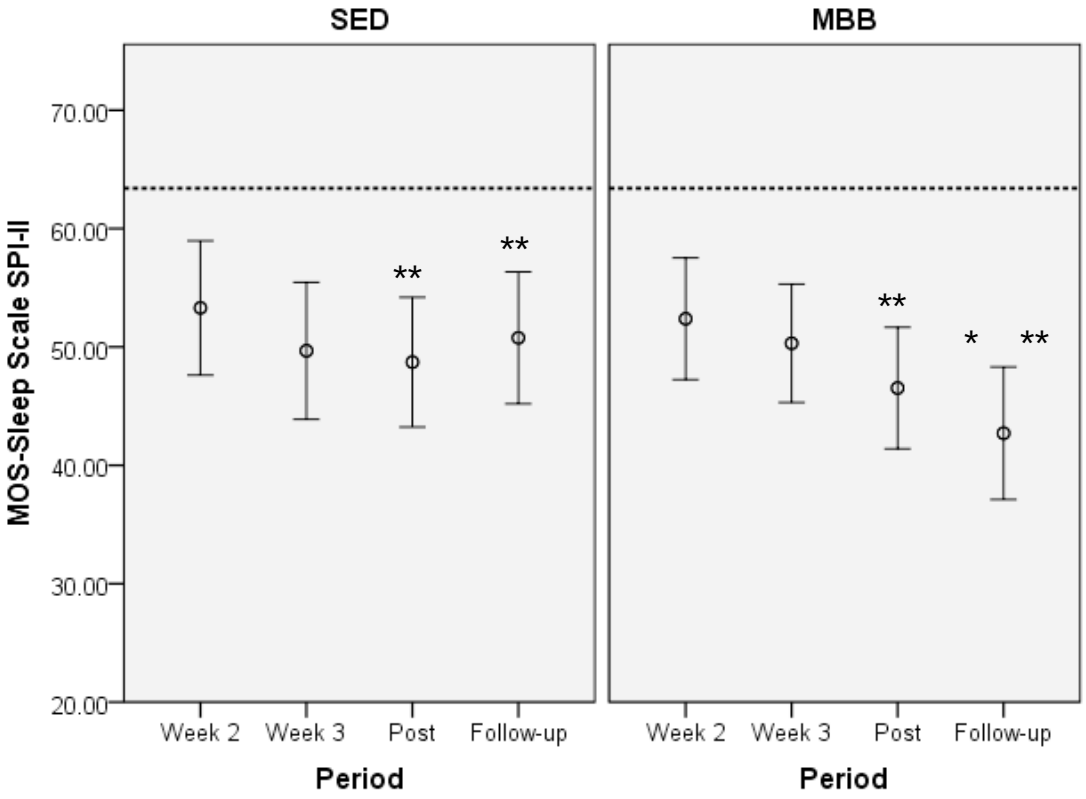

Figure 2. Effects of SED and MBB interventions on sleep (MOS-Sleep Scale–SPI-II).

Note. Estimated means (with 95% Confidence Intervals; CIs), adjusted for pre-intervention baseline (Pre) scores are shown. The dashed horizontal line represents the mean baseline covariate value of each scale, representing a common baseline reference across the two intervention groups. MBB scores were lower than SED scores at Follow-up. SED = Sleep Education; MBB = Mind–Body Bridging; MOS = Medical Outcomes Study; SPI-II = Sleep Problems Index - II; *MBB compared with SED (p < .05). **MBB, SED compared with baseline covariate (p < .05).

Figure 3a

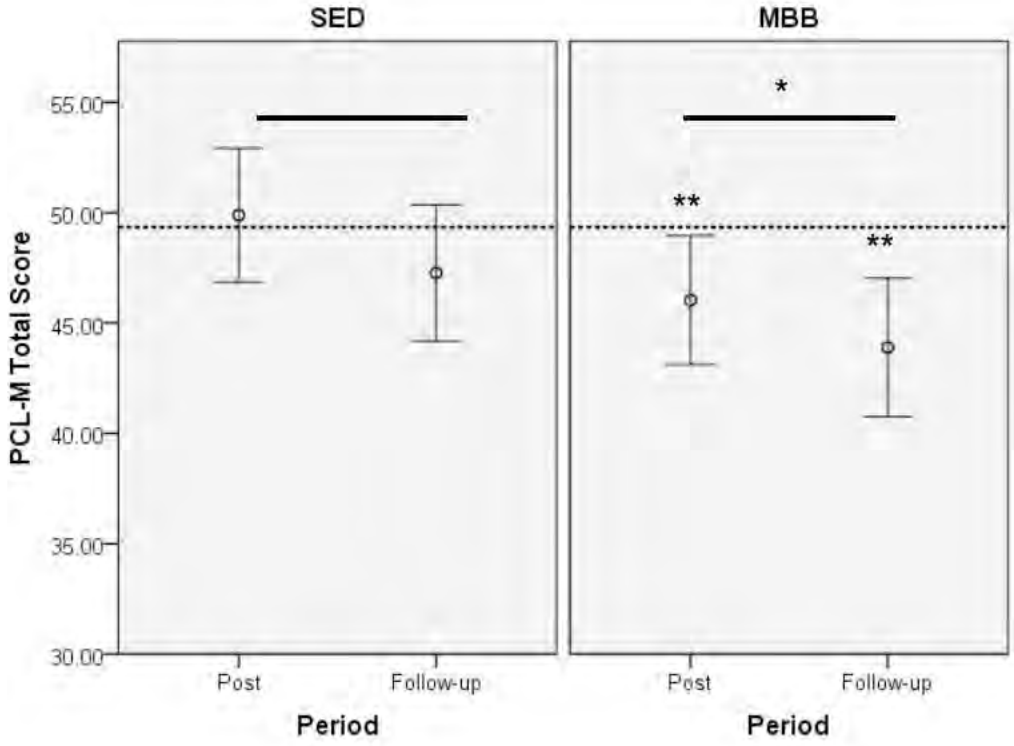
SED
MBB
PCL-M Total Score
55.00
50.00
45.00
40.00
35.00
30.00
*
**
**
Post
Follow-up
Post
Follow-up
Period
Period

Figure 3b

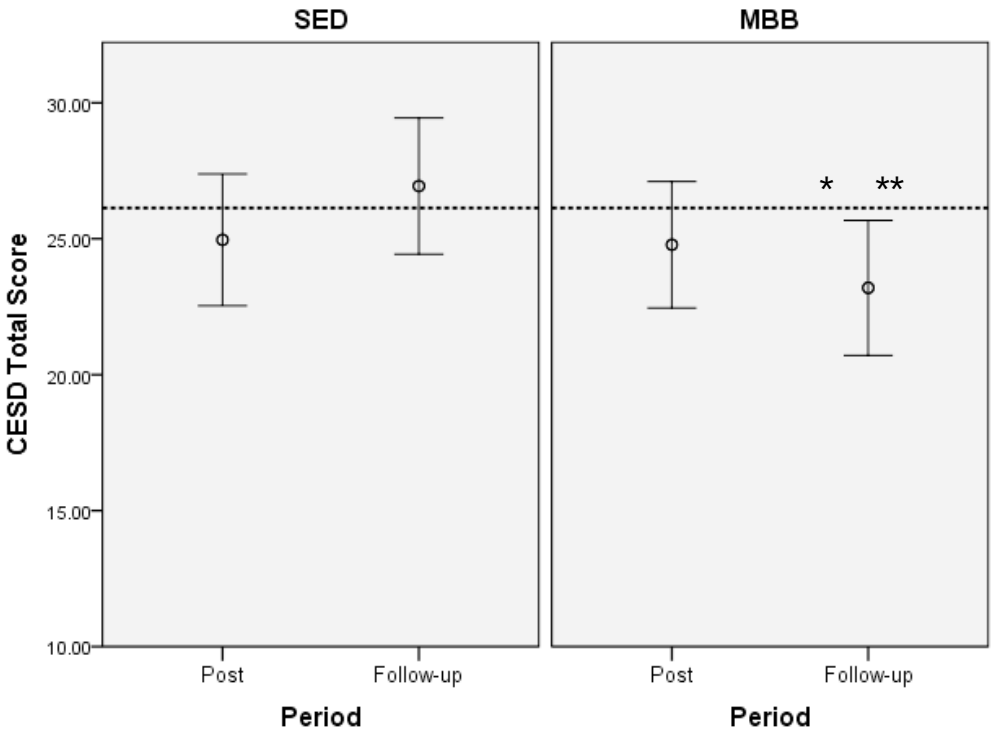
SED
MBB
CESD Total Score
30.00
25.00
20.00
15.00
10.00
*
**
Post
Follow-up
Post
Follow-up
Period
Period

Figure 3c

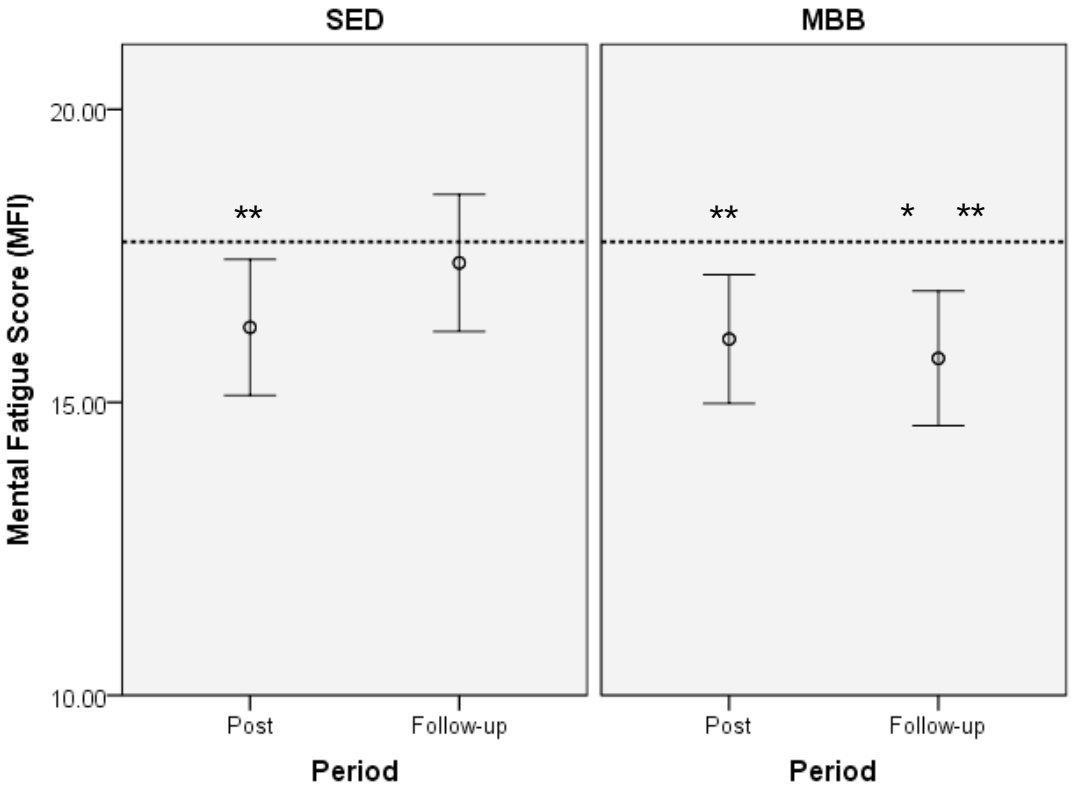

Figure 3a, 3b 3c. Effects of SED and MBB interventions on: a) PTSD (PCL-M Total score), b) Depression (CESD Total core), and c) Mental Fatigue (MFI – Mental Fatigue subscale)

Note. Estimated means (with 95% Confidence Intervals; CIs), adjusted for pre-intervention baseline (Pre) scores are shown. The dashed horizontal line represents the mean baseline covariate value of each scale, representing a common baseline reference across the two intervention groups. MBB scores were lower than SED scores for the overall Treatment effect (PCL-M), and at Follow-up (CES-D, MFI Mental Fatigue subscale). SED = Sleep Education; MBB = Mind–Body Bridging; PCL-M = PTSD Checklist – Military; CES-D Center for Epidemiological Studies – Depression; MFI = Multidimensional Fatigue Inventory; *MBB compared with SED ($p < .05$). **MBB, SED compared with baseline covariate ($p < .05$).

Table 1: Baseline demographics for participants

	SED		MBB	
N	27		33	
	Mean (SD)		**Mean (SD)**	
Age	52.6 (7.2)		49.18 (7.2)	
Months in PGW	7.19 (3.73)		7.35 (4.01)	
Months of Service	7.69 (3.5)		7.36 (3.05)	
Years in Military	16.98 (8.23)		13.62 (7.79)	
	Number of participants	**%**	**Number of participants**	**%**
GENDER				
Female	3	11.1	3	9.1
Male	24	88.9	30	90.9
BRANCH OF MILITARY	(some reported more than one branch)			
Army	18	60.0	17	47.2
Air Force	6	20.0	7	19.4
Navy	2	6.7	9	25.0
Marine	4	13.3	3	8.3
HAZARDOUS EXPERIENCE				
Yes	15	57.7	18	54.5
NO	11	42.3	15	45.5
ETHNICITY				
Hispanic/Latino	2	7.7	3	9.4
Not Hispanic/Latino	24	92.3	29	90.6
RACE				
Asian	0	0	0	0
White	23	88.5	28	87.5

Native Hawaiian/Pacific Islander	0	0	0	0
African American/Black	2	7.7	2	6.3
American Indian/Alaska Native	1	3.8	1	3.1
Other	0	0	1	3.1
EDUCATION				
Less than High School	0	0	0	0
High School Graduate	1	3.7	3	9.1
Associate Degree	2	7.4	10	30.3
Some College	12	44.4	10	30.3
College Degree	8	29.6	8	24.2
Masters or Higher	4	14.8	2	6.1
MARITAL STATUS				
Singe (never married)	5	18.5	7	21.2
Married	16	59.3	14	42.4
Separated/Divorced	5	18.5	11	33.3
Widowed	1	3.7	1	3.0
LIVING SITUATION (could be living with spouse and children/other)				
Alone	5	18.5	11	33.3
Spouse	18	66.7	18	54.5
Children	10	37.0	7	21.2
Other	4	14.8	5	15.2
EMPLOYMENT				
Full time	15	55.6	12	36.4
Part time	2	7.4	5	15.2
Unemployed	4	14.8	2	6.1
Homemaker	0	0	0	0
Retired	6	22.2	6	18.2
Other	0	0	8	24.2

WORKERS COMPENSATION AND DISABILITY DATA				
Receiving Workers Compensation	0	0	0	0
Receiving Long-term Disability				
Yes	13	48.1	24	72.7
No	13	48.1	9	27.3
Missing	1	3.7	0	0
Source of Disability Compensation				
VA	14	51.9	24	72.7
Other	0	0	0	0.0
Responding No to previous item	13	48.1	9	27.3
Pending Disability				
Yes	10	37.0	12	36.4
No	17	63.0	19	57.6
Missing	0	0	2	6.1
Source of Pending Disability				
VA	9	33.3	11	33.3
Other	1	3.7	1	3.0
Responding No to previous item	17	63.0	21	63.6

Table 2: Unadjusted means (and 95% Confidence Intervals) of Self-Reported Primary Outcome Measures for Comparisons between Mind-Body Bridging (MBB) and Sleep Education (SED) in Gulf War Veterans.

		SED		MBB			
OUTCOME MEASURE	**Period**	**Mean**	**95% CI (lower, upper)**	**Mean**	**95% CI (lower, upper)**	**p-value**	**Effect size[a]**
MOS-Sleep Scale: Sleep Problems Index-II	**Pre**	63.67	(58.48, 68.86)	64.55	(58.68, 70.41)	.32*	
	Week 1	61.67	(54.99, 68.35)	59.57	(54.18, 64.95)		
	Week 2	55.27	(48.37, 62.17)	51.83	(44.67, 58.98)		
	Week 3	52.03	(45.08, 58.98)	49.67	(43.18, 56.15)		
	Post	50.21	(44.09, 56.33)	45.12	(38.16, 52.08)		.38
	Foll-up	52.18	(43.63, 60.72)	41.32*****	(34.13, 48.52)	.046**	.70
MOS-Sleep Scale: Sleep Problems Index-I	**Pre**	62.60	(57.25, 67.96)	63.13	(57.32, 68.94)	.34*	
	Week 1	60.06	(53.25, 66.88)	57.89	(52.65, 63.12)		
	Week 2	55.42	(48.16, 62.68)	50.95	(43.87, 58.03)		
	Week 3	51.88	(44.20, 59.57)	48.89	(42.29, 55.49)		
	Post	50.38	(44.01, 56.76)	45.60	(38.80, 52.39)		
	Foll-up	50.00	(40.97, 59.03)	40.43	(33.20, 47.67)	.08**	
MOS-Sleep Scale: Sleep Disturbance	**Pre**	66.02	(57.77, 74.26)	68.26	(60.43, 76.09)	.36*	
	Week 1	63.56	(53.85, 73.26)	64.32	(56.22, 72.42)		
	Week 2	54.05	(44.68, 63.41)	55.98	(46.99, 64.97)		
	Week 3	49.64	(41.22, 58.06)	50.82	(42.11, 59.53)		
	Post	49.13	(39.97, 58.30)	42.66	(33.58, 51.75)		
	Foll-up	53.08	(43.54, 62.62)	41.56	(31.06, 52.06)	.07**	
MOS-Sleep Scale: Sleep Adequacy	**Pre**	27.78	(19.62, 35.94)	26.67	(18.61, 34.73)	.21*	
	Week 1	29.23	(18.70, 39.76)	29.39	(21.42, 37.37)		

	Week 2	31.67	(21.65, 41.68)	33.57	(25.11, 42.03)	
	Week 3	27.39	(17.79, 36.99)	34.00	(25.70, 42.30)	
	Post	29.23	(21.57, 36.89)	31.95	(23.26, 40.63)	
	Foll-up	34.40	(22.48, 46.32)	43.48	(34.29, 52.66)	.07**
MOS-Sleep Scale: Somnolence	**Pre**	53.36	(44.09, 62.62)	52.32	(44.50, 60.14)	.91*
	Week 1	53.59	(44.09, 63.09)	44.65	(37.17, 52.13)	
	Week 2	45.28	(35.01, 55.55)	35.95	(27.41, 44.49)	
	Week 3	42.03	(34.79, 49.27)	36.67	(29.45, 43.88)	
	Post	37.44	(28.85, 46.02)	33.56	(25.74, 41.38)	
	Foll-up	42.67	(33.89, 51.44)	33.62	(25.22, 42.03)	
MOS-Sleep Scale: Shortness of Breath	**Pre**	39.26	(24.96, 53.56)	41.21	(31.04, 51.39)	.99*
	Week 1	36.92	(23.86, 49.99)	34.85	(24.43, 45.27)	
	Week 2	35.83	(23.39, 48.28)	26.43	(15.86, 36.99)	
	Week 3	21.74	(9.81, 33.66)	26.67	(15.87, 37.47)	
	Post	23.85	(12.65, 35.04)	21.50	(13.65, 29.35)	
	Foll-up	25.60	(14.29, 36.91)	20.00	(10.60, 29.40)	
MOS-Sleep Scale: Snoring	**Pre**	54.07	(39.55, 68.60)	62.50	(49.07, 75.93)	.88*
	Week 1	57.69	(44.11, 71.27)	58.71	(44.93, 72.49)	
	Week 2	51.67	(36.33, 67.00)	52.86	(38.51, 67.21)	
	Week 3	53.91	(38.17, 69.65)	50.71	(35.72, 65.71)	
	Post	43.85	(29.39, 58.30)	57.93	(42.76, 73.09)	
	Foll-up	53.60	(38.39, 68.81)	57.39	(41.90, 72.89)	

[a]Effect size (Cohen's d) calculated for the difference between the two interventions at (change from baseline) Post or Follow-up, respectively;
*For Treatment; **Treatment by Period at Follow-up.

Table 3: Unadjusted means (and 95% Confidence Intervals) of Self-Reported Outcome Measures for Comparisons between Mind-Body Bridging (MBB) and Sleep Education (SED) in Gulf War Veterans.

		SED		MBB			
OUTCOME MEASURE	**Period**	**Mean**	**95% CI (lower, upper)**	**Mean**	**95% CI (lower, upper)**	**p-value**	**Effect size[a]**
PTSD (PCL-M TOTAL SCORE)	**Pre**	49.63	(43.60, 55.66)	52.76	(47.53, 57.98)	**.04***	
	Post	49.38	(43.00, 55.77)	46.88	(40.94, 52.81)	.07[#] (post)	.07
	Foll-up	46.96	(39.72, 54.20)	43.54	(37.44, 49.64)		.19
DEPRESSION (CESD TOTAL SCORE)	**Pre**	26.21	(23.18, 29.24)	27.36	(25.20, 29.53)	.17*	
	Post	24.85	(21.49, 28.22)	25.39	(22.47, 28.32)		.08
	Foll-up	26.96	(22.57, 31.36)	22.83	(20.45, 25.22)	**.04[##] (foll-up)**	.71
QUALITY OF LIFE (SF-36 TOTAL SCORE)	**Pre**	42.96	(35.83, 50.09)	43.75	(38.62, 48.89)	.87*	
	Post	46.40	(39.56, 53.23)	48.35	(42.62, 54.08)		.37
	Foll-up	44.18	(35.82, 52.53)	48.20	(41.98, 54.43)		.42
QUALITY OF LIFE (SF-36 PAIN)	**Pre**	37.87	(29.51, 46.23)	38.86	(30.75, 46.97)	.55*	
	Post	39.13	(29.99, 48.28)	46.61	(37.86, 55.35)		.29
	Foll-up	39.50	(28.58, 50.42)	45.00	(36.55, 53.45)		.20
BRIEF SYMPTOM INVENTORY (GLOBAL SEVERITY INDEX)	**Pre**	25.37	(20.30, 30.43)	24.75	(20.48, 29.02)	.51*	
	Post	20.38	(14.12, 26.63)	23.04	(18.16, 27.92)		.27 (SED)
	Foll-up	23.52	(16.09, 30.94)	20.22	(15.56, 24.87)		.27
MULITDIMENSIONAL FATIGUE INVENTORY (GENERAL FATIGUE)	**Pre**	20.65	(19.34, 21.96)	20.97	(20.08, 21.85)	.27*	
	Post	20.00	(18.66, 21.34)	19.44	(18.08, 20.80)		.25
	Foll-up	20.18	(18.42, 21.95)	18.81	(17.27, 20.35)		.49
MULITDIMENSIONAL FATIGUE INVENTORY	**Pre**	17.39	(15.86, 18.92)	18.31	(17.17, 19.45)	.23*	
	Post	16.22	(14.52, 17.92)	16.20	(14.66, 17.74)	**.03****	.18

	Foll-up	17.09	(15.43, 18.75)	16.10	(14.50, 17.69)	**.05**[##]	.47
COGNITIVE FAILURE (CFQ TOTAL SCORE)	**Pre**	55.88	(46.17, 65.60)	57.09	(51.70, 62.48)	.44*	
	Post	46.00	(35.05, 56.95)	49.85	(42.36, 57.34)		.16
	Foll-up	46.71	(35.57, 57.86)	50.59	(40.60, 60.58)		.15
MINDFULNESS (FFMQ TOTAL SCORE)	**Pre**	117.26	(107.86, 126.66)	118.97	(111.40, 126.54)	.67*	
	Post	122.46	(110.66, 134.26)	125.32	(116.63, 134.02)		.05
	Foll-up	121.56	(109.94, 133.18)	125.92	(116.21, 135.62)		.11

[a]Effect size (Cohen's d) calculated for the difference between the two interventions at (change from baseline) Post or Follow-up, respectively
*For Treatment; **For Treatment by Period Interaction
[#] Treatment by Period Interaction, Post; [##] Treatment by Period Interaction, Follow-up

Table 4: Changes in physical and psychological symptoms following post assessment clinical evaluation for comparisons between SED and MBB in Gulf War Veterans.

	SED		MBB	
	No. participants	**Percentage**	**No. participants**	**Percentage**
PHYSICAL CONDITION				
Worsened	2	9.09	1	4.00
No Change	17	77.27	16	64.00
Improved	3	13.64	8	32.00
TOTAL	22	100.00	25	100.00
SLEEP				
Worsened	3	11.54	2	6.90
No Change	16	61.54	10	34.48
Improved	7	26.92	17	58.62
TOTAL	26	100.00	29	100.00
FATIGUE				
Worsened	1	4.00	1	3.85
No Change	20	80.00	17	65.38
Improved	4	16.00	8	30.77
TOTAL	25	100.00	26	100.00
HEADACHE				
Worsened	1	4.17	1	3.85
No Change	20	83.33	17	65.38
Improved	3	12.50	8	30.77
TOTAL	24	100.00	26	100.00
PAIN				
Worsened	5	19.23	1	3.57
No Change	20	76.92	21	75.00

Improved	1	3.85	6	21.43
TOTAL	26	100.00	28	100.00
BREATHING				
Worsened	2	8.33	2	8.70
No Change	20	83.33	16	69.57
Improved	2	8.33	5	21.74
TOTAL	24	100.00	23	100.00
GASTRO-INTESTINAL SYMPTOMS				
Worsened	2	9.09	1	4.17
No Change	20	90.91	20	83.33
Improved	0	0.00	3	12.50
TOTAL	22	100.00	24	100.00
COGNITIVE ABILITY				
Worsened	1	4.35	4	17.39
No Change	19	82.61	14	60.87
Improved	3	13.04	5	21.74
TOTAL	23	100.00	23	100.00
MEMORY AND CONCENTRATION				
Worsened	3	13.04	1	3.70
No Change	16	69.57	19	70.37
Improved	4	17.39	7	25.93
TOTAL	23	100.00	27	100.00
OVERALL SLEEP AND GULF WAR ILLNESS SYMPTOMS				
Worsened	6	23.08	4	13.79
No Change	11	42.31	7	24.14
Improved	9	34.62	18	62.07
TOTAL	26	100.00	29	100.00

PSYCHOLOGICAL STATE				
Worsened	2	8.00	1	3.45
No Change	17	68.00	16	55.17
Improved	6	24.00	12	41.38
TOTAL	25	100.00	29	100.00